

How to Use the American Diabetes Association's Type 2 Diabetes Algorithm

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 American Diabetes Association.

Disclosures of Interest

- **I have no conflicts**

 American Diabetes Association.

Key points to emphasize

New information -- Updated October 5, 2018 at EASD meeting in Berlin

1. Update informed by evidence generated in the past 2 years
2. Greater focus on lifestyle interventions, with increased emphasis on weight loss and obesity management, including metabolic surgery
3. Greater focus on patient related issues and self-management which have a major impact on success of any pharmacological interventions
4. Preferred choices of glucose-lowering agents driven by new evidence from CVOT and consideration of areas of major clinical need (for example weight and risk of hypoglycemia)
5. GLP-1 RAs are preferred to insulin as first injectable

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Balancing Risks and Benefits for Personalized Goals

More Stringent Control

- No hypoglycemia
- Less complexity/polypharmacy
- Lifestyle or metformin only
- Short disease duration
- Long life expectancy
- No CVD



Less Stringent Control

- History of severe hypoglycemia
- High burden of therapy
- Longer disease duration
- Limited life expectancy
- Extensive co-morbidity
- CVD

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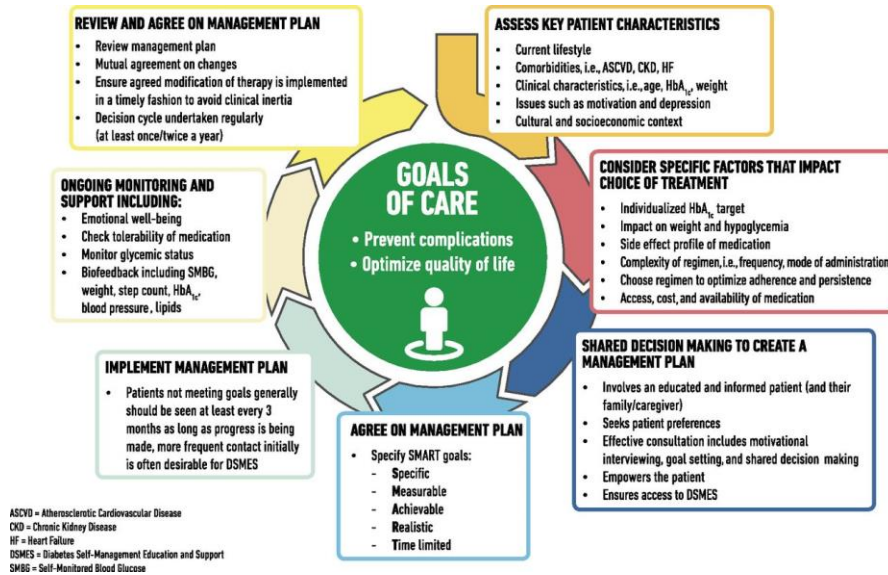
Improving Glycemic Management

- Focus on treatments for glycemic control
 - Behavioral approaches
 - Medications
 - Metabolic surgery
- Address increasing complexity of patient centered therapeutic decisions in the context of expanding therapeutic options and new information on benefits and risks

Putting the Patient at the Center of Care



Decision cycle for patient-centered glycemic management in type 2 diabetes.



Shared decision making in type 2 diabetes

SDM can improve

- decision quality
- patient knowledge
- patient risk perception

Ethical imperative for support of patients' autonomy

Diabetes Self-Management Education and Support (DSMES)

- Is available to patients at critical times
- Individualized to the needs of the person, including language and culture
- Structured theory-driven written curriculum with supporting materials
- Delivered in group or individual settings by trained educators
- Promote healthy eating, physical activity, good medication-taking behavior, and increase self-efficacy
- Supports person and their family in developing attitudes, beliefs, knowledge and skills to self-manage diabetes
- Includes core content and monitoring of patient progress, including health status, quality of life.
- Evidence-based

Empathic patient-centered care

- Patients with diabetes often live with multiple chronic conditions
- Providers & health care systems should prioritize the delivery of empathic, individualized patient-centered care
- To determine what is the best management option for each patient, consider each individual's
 - personal, social and biomedical context,
 - his/her values,
 - reasons he/she values the available options, and
 - relative contribution of each option in terms of benefits, harms, costs and inconveniences.

Persistence and medication adherence

- Mean medication adherence rate \approx 75%, average proportion of patients adherent to medication < 70%.
- Adherence slightly varies between orals vs injectable therapy and individual classes
- Discontinuation rates range from 10% to 60% (both in observational studies and in clinical trials)

Clinical Inertia

Clinical inertia: failure of healthcare providers to initiate or intensify therapy when indicated, due to:

- overestimation of care provided
- use of “soft” reasons to avoid intensification of therapy
- lack of education, training, and practice organization aimed at achieving therapeutic goals

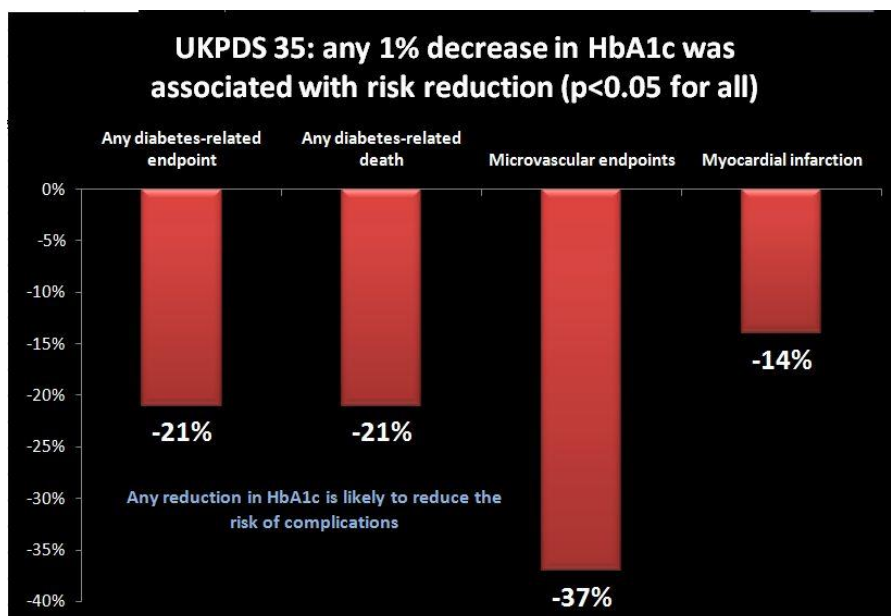
Glucose-Lowering Medication in Type 2 diabetes: overall approach

Foundational therapy is metformin and comprehensive lifestyle management (including weight management and physical activity)

Metformin is the preferred initial glucose lowering medication for most people with T2D

This recommendation is based on the efficacy, safety, tolerability, and extensive clinical experience with this medication. Results from UKPDS showed benefits of initial treatment with metformin in clinical outcomes related to diabetes, with less hypoglycemia and weight gain than with insulin or sulfonylureas.

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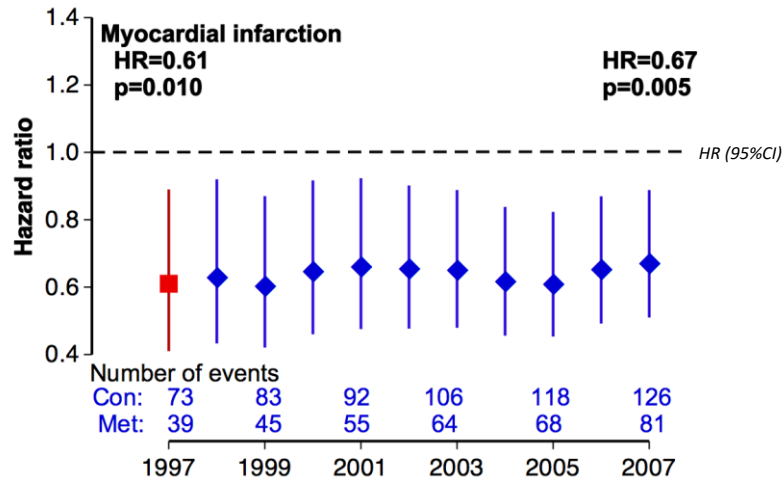


 American Diabetes Association.

British Medical Journal 2000; 321: 405-412

(fatal or non-fatal myocardial infarction or sudden death)

Intensive (metformin) vs. Conventional glucose control



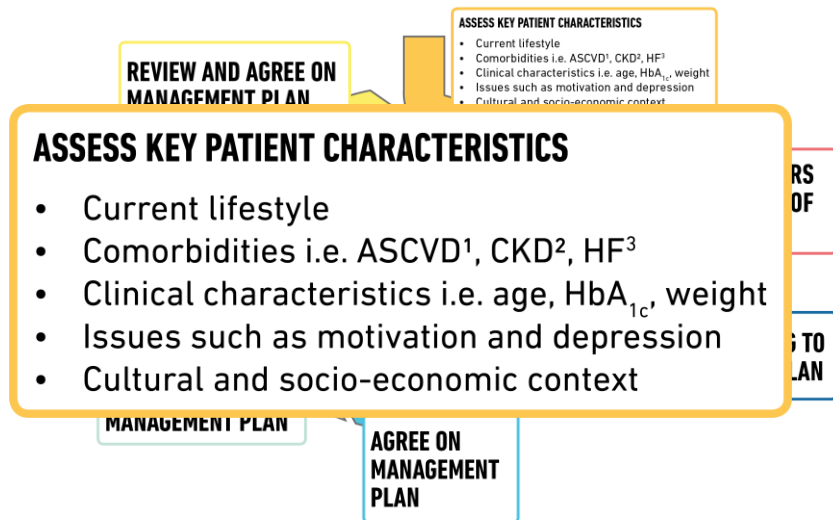
Metformin Monotherapy

1. Recommended dosage 1000 mg BID (if tolerated)
2. Titrate slowly over 1-2 weeks (500 mg increments and always with food)
3. Use of extended release **highly recommended**
4. Continue full dosing if GFR > 45 cc/min
5. Reduce to 500 mg BID if GFR 30-45 cc/min
6. STOP Metformin if GFR less than 30

Recommended Process for Glucose Lowering Medication Selection: Where Does New Evidence From Cardiovascular Outcome Trials Fit In ?

Figure 1

DECISION CYCLE FOR PATIENT-CENTRED GLYCAEMIC MANAGEMENT IN TYPE 2 DIABETES



Foundational therapy is metformin and comprehensive lifestyle management (including weight management and physical activity)

Step 1: Assess cardiovascular disease

Presence of cardiovascular disease is compelling indication

ASCVD predominates



HF or CKD predominates





The NEW ENGLAND
JOURNAL of MEDICINE

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes
N Engl J Med 2016;375:311-22.

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes
N Engl J Med 2016;375:1834-44.

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes
N Engl J Med 2015;373:2117-28

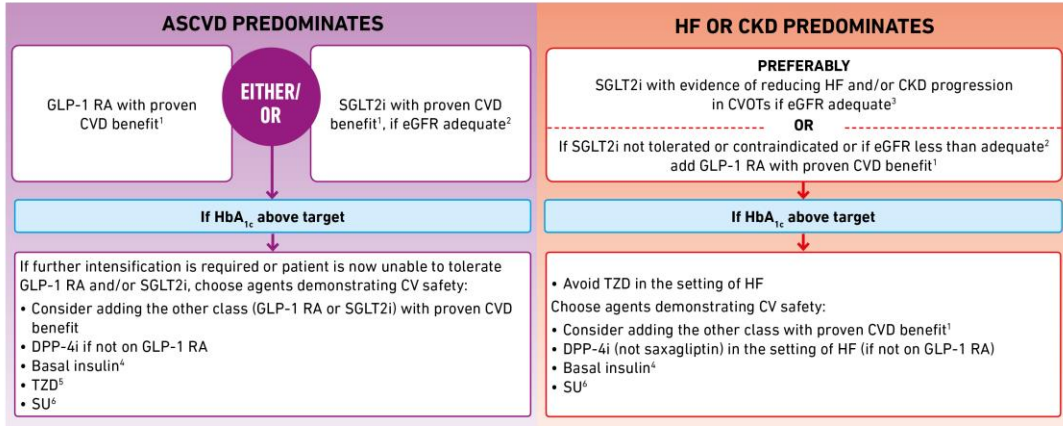
Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes
N Engl J Med 2017;377:644-57.

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes
N Engl J Med 2019;380:347-57..

Considerations

- ASCVD is defined differently across trials
 - Established CVD (e.g. MI, stroke, revascularization procedure)
 - Very high cardiovascular risk
- Each cardiovascular outcomes trial, while large, is a single experiment
- It is not always clear whether differences in trial findings within a drug class are related to trial design or to true differences in the individual medications
 - Where evidence suggests a hierarchy, this is noted

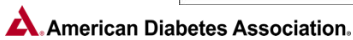
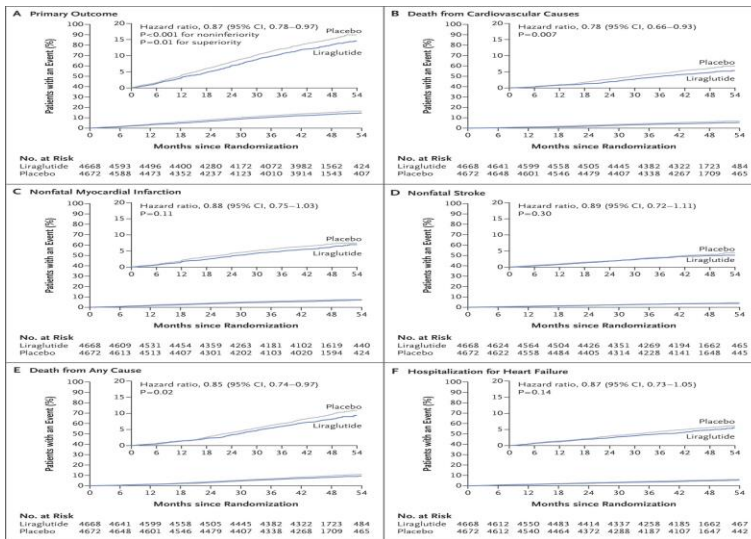
CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED ASCVD OR CKD



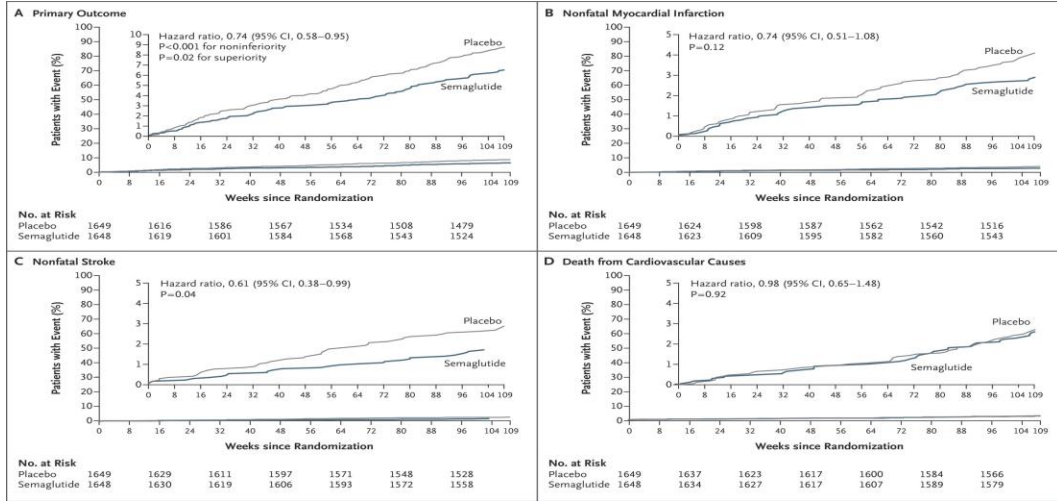
1. Proven CVD benefit means it has label indication of reducing CVD events. The GLP-1 RA strongest evidence of liraglutide + saxagliptin is available for SGLT2i evidence indirectly through for empagliflozin + saxagliptin.
 2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use.
 3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs.
 4. Dapagliflozin or HF (dapagliflozin) have demonstrated CV safety.
 5. Low dose may be better tolerated though low will still reduce the CVD effects.
 6. Cholesterol generation SU with lower risk of hypoglycemia.



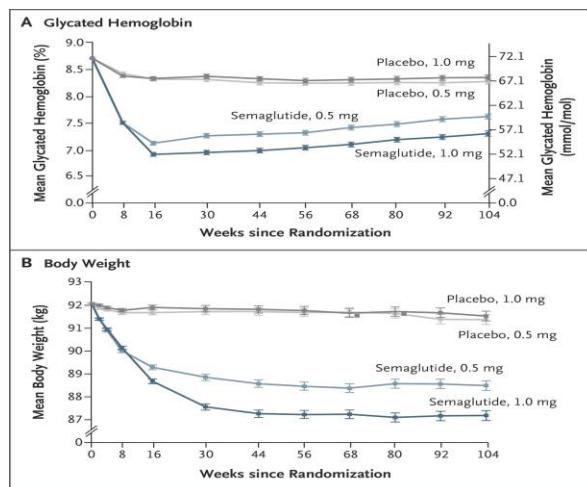
Liraglutide and CVOT



Semaglutide and CVOT



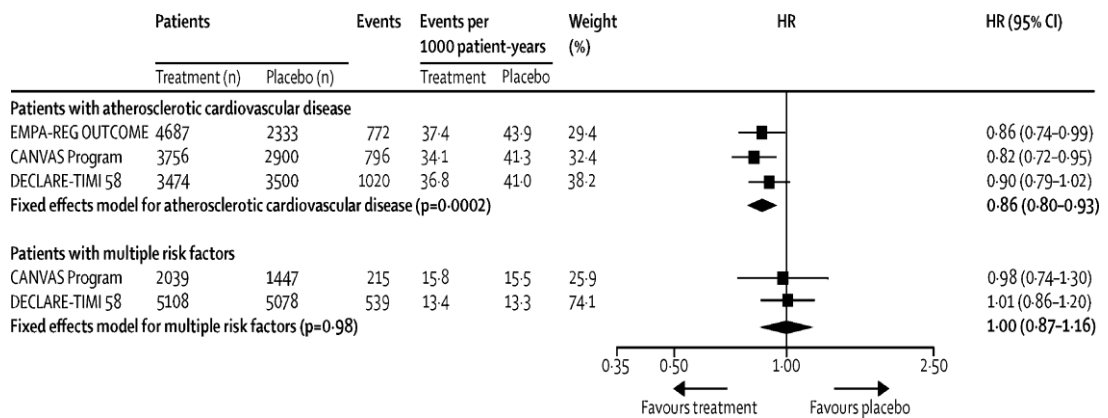
Semaglutide and HbA1c/Weight



GLP-1 and CVOT

	Lixisenatide	Liraglutide	Semaglutide	Exenatide
3 pt MACE	1.02 0.89-1.17	0.87 0.78-0.97	0.74 0.58-0.95	0.91 0.83-1.00
CV Death	0.98 0.78-1.22	0.78 0.66-0.93	0.98 0.65-1.48	0.88 0.76-1.02
Non-fatal MI	1.03 0.87-1.22	0.88 0.75-1.03	0.74 0.51-1.08	0.97 0.85-1.10
Non-fatal stroke	1.12 0.79-1.58	0.89 0.72-1.11	0.61 0.38-0.99	0.85 0.70-1.03
HF Hospitalization	0.96 0.75-1.23	0.87 0.73-1.05	1.11 0.77-1.61	0.94 0.78-1.13
All cause mortality	0.94 0.78-1.13	0.85 0.74-0.97	1.05 0.74-1.50	0.86 0.77-0.97

SGLT2i and MACE



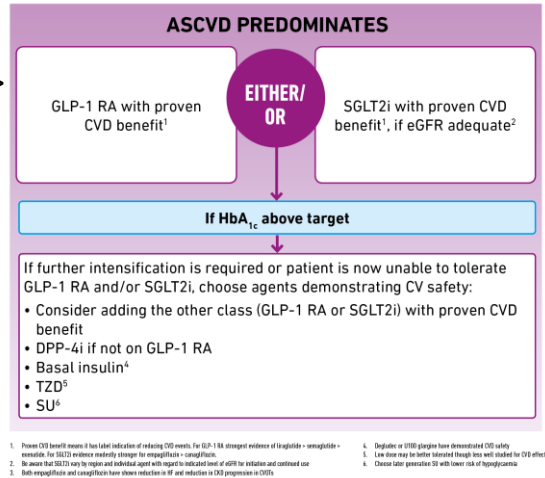
If ASCVD Predominates:

GLP-1 RA with proven cardiovascular benefit

- Strongest evidence for liraglutide > semaglutide > exenatide LAR

SGLT2-i with proven cardiovascular benefit

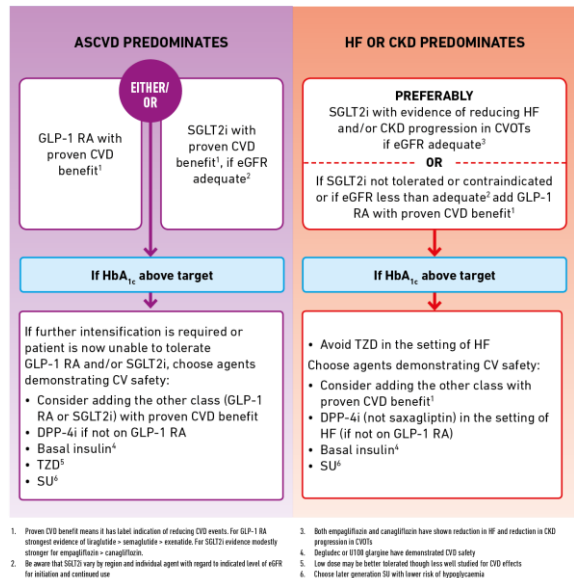
- Modest evidence for empagliflozin > canagliflozin



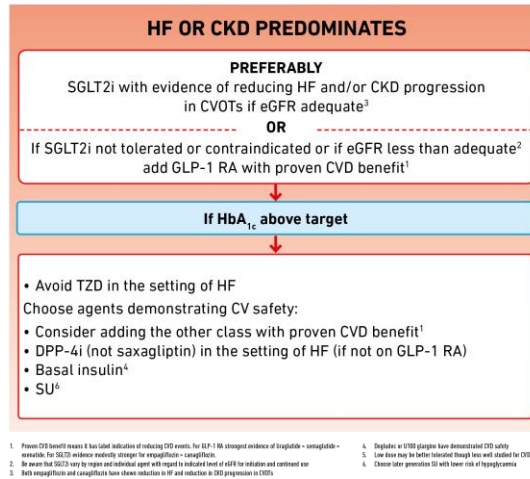
Caveats and Questions

No evidence of CVD benefit in those at lower cardiovascular risk

The combination of SGLT2-i and GLP-1 RA has not been tested in cardiovascular outcome trials



CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED HF OR CKD



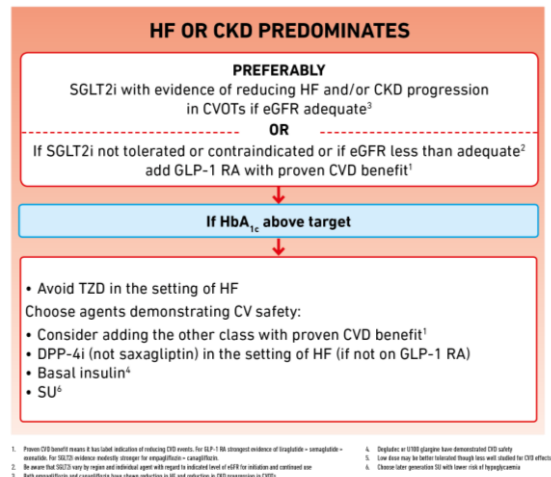
Among patients with ASCVD in whom HF coexists or is of concern, SGLT2 inhibitor are recommended

Rationale: Patients with T2D are at increased risk for heart failure with reduced or preserved ejection fraction

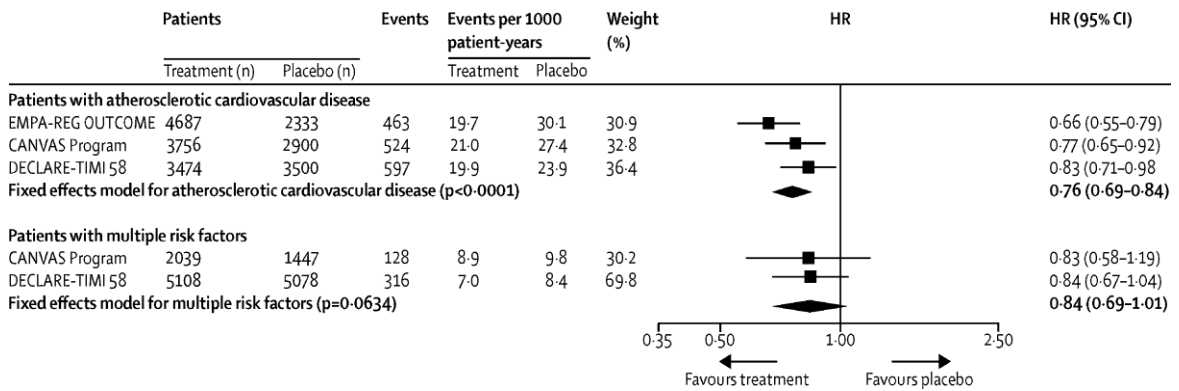
Significant, consistent reductions in hospitalization for heart failure have been seen in SGLT2-i trials

Caveat: trials were not designed to adjudicate heart failure

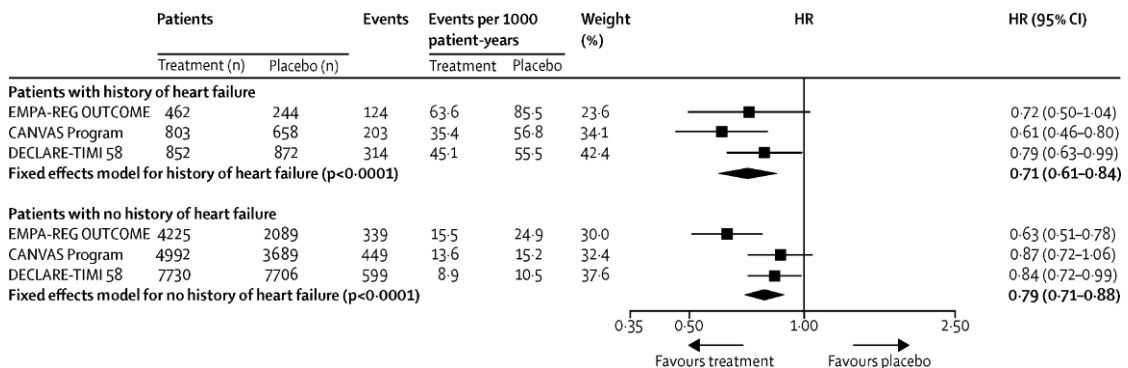
Majority of patients did not have clinical heart failure at baseline



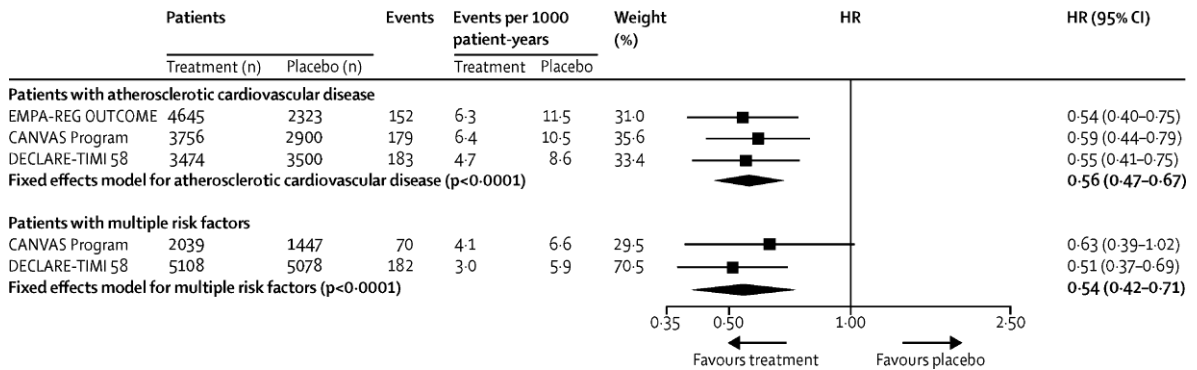
SGLT2i and Heart Failure



SGLT2i and Heart Failure



SGLT2i and Renal Progression

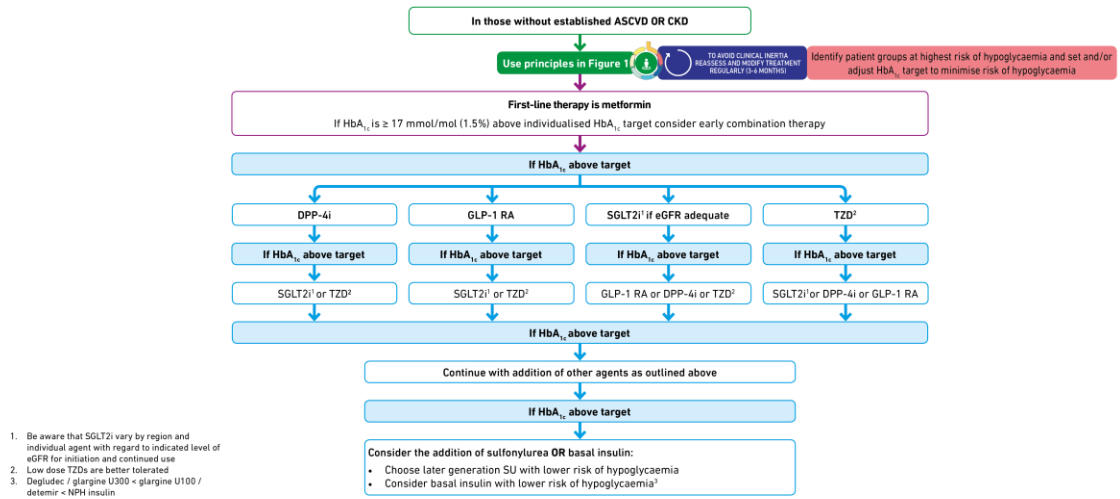


Recommendation:

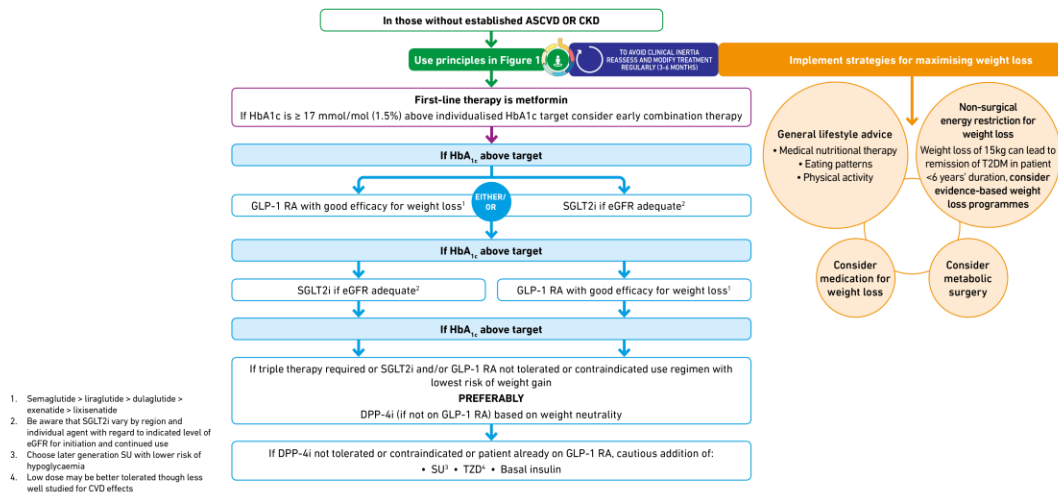
For patients with type 2 diabetes and chronic kidney disease, consider use of a sodium–glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist shown to reduce risk of chronic kidney disease progression, cardiovascular events, or both. **C**

Several of these medications have demonstrated renal benefit and cardiovascular benefit and should be considered as part of treatment.

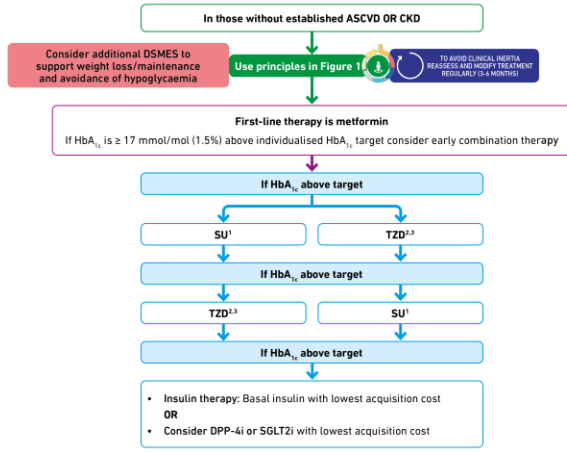
CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMISE HYPOGLYCAEMIA



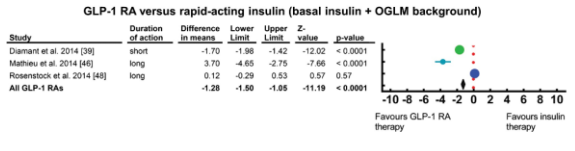
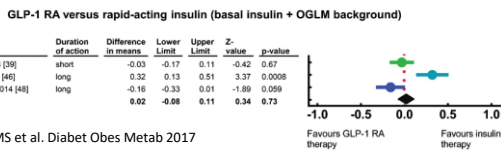
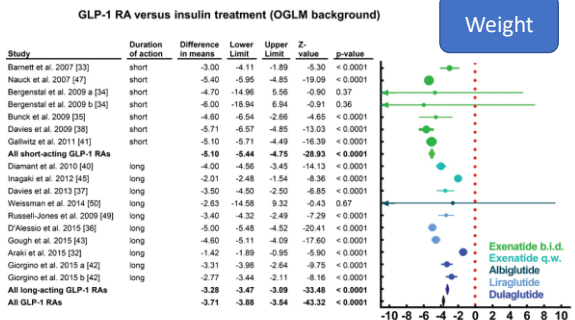
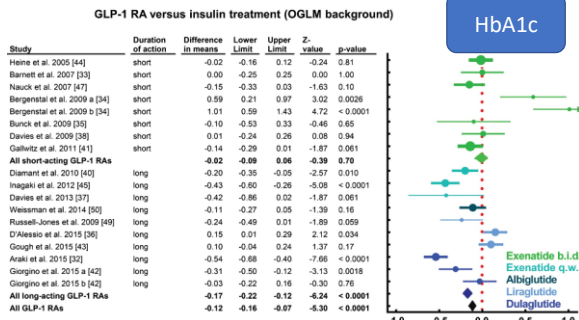
CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMISE WEIGHT GAIN OR PROMOTE WEIGHT LOSS



CHOOSING GLUCOSE-LOWERING MEDICATION IF COST IS A MAJOR ISSUE



Consensus Recommendation: In patients who need the greater glucose-lowering effect of an injectable medication, **GLP-1 receptor agonists are the preferred choice to insulin**. For patients with extreme and symptomatic hyperglycaemia, insulin is recommended.

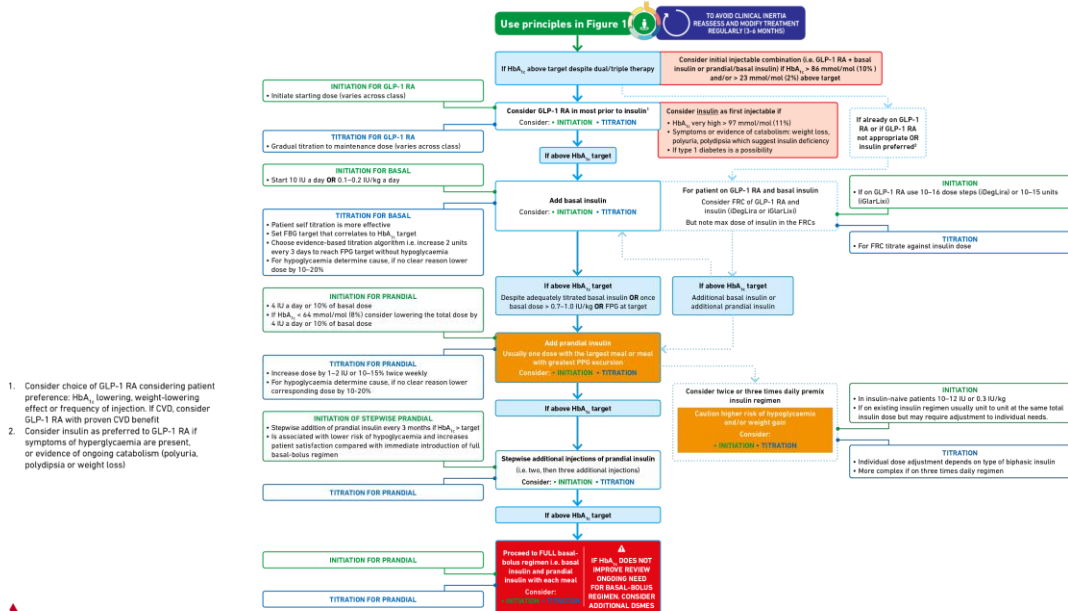


Abd El Aziz MS et al. Diabet Obes Metab 2017



Figure 7

INTENSIFYING TO INJECTABLE THERAPIES



Case Study

- **Patient:** Ms. F
- **Age:** 57
- **Occupation:** CEO of local non-for-profit
- **Diabetes Hx:** 6 years; BMI 27; no cx; struggles with weight, eats out frequently, daily schedule
- **Current Meds:** metformin, saxagliptin, insulin detemir 36 units HS
- **A1C:** 8.1%, anti-GAD negative, eGFR >60 ml/min/1.73m
- **BG pattern:** fasting average 142 mg/dL, post-meal average 207 mg/dL, no hypoglycemia
- **Patient/Provider Goals:** avoid complications, facilitate weight loss, dosing simplicity

Strategy for Ms F

- Ensure she has received (adequate) DSMES
- Maximize metformin (if not already)
- Consider GLP-1 as next step
- D/C DPP4i if add GLP-1
- Taper insulin if possible. Consider switch to longer acting insulin or give detemir BID if insulin still needed and insurance dictates choice

Case Study

- **Patient:** Mrs. L
- **Age:** 77
- **Occupation:** retired teacher
- **Diabetes Hx:** 12 years, no retinopathy, no nephropathy, no neuropathy sx, SU caused hypoglycemia, SGLT2-i yeast infections, pioglitazone edema
Cardiovascular History: none
- **Current Diabetes Meds:** metformin 500mg BID, pioglitazone 30 mg daily
- **A1C:** 8.3%
- **BG pattern:** fasting average 145 mg/dL, post-meal average 200 mg/dL, infrequent hypoglycemia
- **Patient/Provider Goals:** healthy aging

Strategy for Mrs L

- Establish HbA1c goal
- Ensure she has received (adequate) DSMES
- Maximize metformin
- D/C pioglitazone
- Consider DPP4i

Case Study

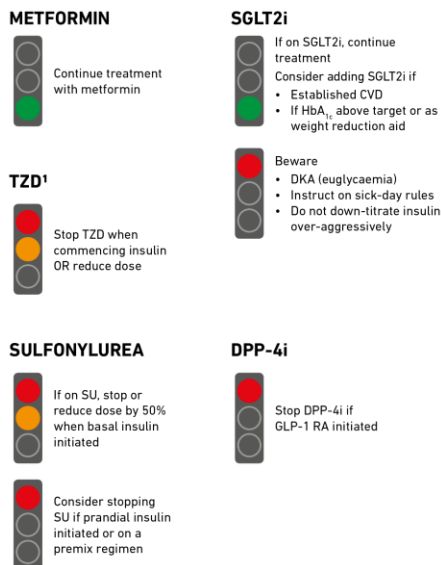
- **Patient:** Mr. K
- **Age:** 51
- **Occupation:** drives a delivery truck
- **Diabetes Hx:** 8 years,; BMI 28; microalbumin/creatinine ratio < 20; + non-proliferative retinopathy, active, eats out every day
- **A1c:** A1C: 9.5%, anti-GAD negative, eGFR >60 ml/min/1.73m²
- **Cardiovascular History:** CVA last year (slurred speech, left-sided weakness) w/ full recovery, stopped smoking
- **Current Diabetes Meds:** metformin 500 mg ER 3 tabs per day, pioglitazone 30 mg daily
- **Cardiovascular Meds:** ARB, statin, ASA
- **BG pattern:** fasting average 160-180 mg/dL, post-meal average 260 mg/dL, no hypoglycemia
- **Patient/Provider Goals:** avoid complications, support healthy eating

Strategy for Mr K

- Establish HbA1c goal
- Encourage lifestyle changes and DSMES
- Maximize metformin
- D/C pioglitazone
- Consider GLP-1 vs basal insulin
- If Hba1c not at goal with changes, consider addition of basal insulin to GLP-1

Figure 8

CONSIDERING ORAL THERAPY IN COMBINATION WITH INJECTABLE THERAPIES



1. Contraindicated in some countries, consider lower dose. This combination has a high risk of fluid retention and weight gain

Recommendations

In most patients who need the greater glucose-lowering effect of an injectable medication, glucagon-like peptide 1 receptor agonists are preferred to insulin. **B**

Intensification of treatment for patients with type 2 diabetes not meeting treatment goals should not be delayed. **B**

The medication regimen should be reevaluated at regular intervals (every 3–6 months) and adjusted as needed to incorporate new patient factors. **E**

Conclusions

An important early step in this new approach: consider the presence or absence of ASCVD, CKD, and heart failure.

In patients with ASCVD, some GLP-1 RA and SGLT2-i are recommended in these patients.

Conclusions

Among patients with atherosclerotic cardiovascular disease at high risk of heart failure or in whom heart failure coexists, sodium–glucose cotransporter 2 inhibitors are preferred.

For patients with type 2 diabetes and chronic kidney disease, consider use of a sodium–glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist shown to reduce risk of chronic kidney disease progression, cardiovascular events, or both.

- Studies of HF or CKD as primary outcome are ongoing with SGLT2-i.

Summary

Consider the presence or absence of ASCVD, CKD and HF

Start with metformin if tolerated, then:



In patients with ASCVD a GLP-1 RA or SGLT2-i is recommended



In patients with HF SGLT2-i is recommended



In patients with CKD, with or without ASCVD consider an SGLT2-i

Agents with proven benefit are preferred

ASCVD, CKD and HF affects choice of additional glucose lowering medication

Thank you